

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty Docket: Van den Brink-1

In re application of:

Gijs R. VAN DEN BRINK *et al.*

Serial No. 10/505,230

Filed: July 1, 2005

For: HEDGEHOG-RELATED PROPHYLAXIS,
THERAPY AND DIAGNOSIS OF GI TRACT
CARCINOGENESIS

Art Unit: 1646

Examiner: Zachary C. HOWARD

Confirmation No. 1902

DECLARATION UNDER 37 C.F.R. § 1.132 OF GIJS R. VAN DEN BRINK

Assistant Commissioner for Patents
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Dear Sir:

I, the undersigned, declare as follows:

1. I am a co-inventor of the above-identified application. I received an M.D. and a Ph.D. degree from the University of Amsterdam in 1998 and 2002, respectively. I began working on in the field of gastroenterology on the basic biology of the gastrointestinal (GI) tract in 1998. My current emphasis is on the genetics and biology of GI cancer development and therapy. Currently, I am the Chief of the Laboratory of Gastroenterology & Hepatology at the Leiden University Medical Center in the Netherlands. I am an author of over 40 published papers and book chapters in my field. A copy of my *Curriculum Vitae* is attached to this Declaration as Appendix 2.

2. After the priority date and filing date of the above-identified patent application, I and my colleagues conducted experiments to test the ability of recombinant Hedgehog protein to prevent development of intestinal/colorectal cancer as discussed in the patent application. To this end, we transformed *Lactococcus lactis* (LL) bacteria (also referred to as “transgenic” bacteria) so that they secreted recombinant murine sonic hedgehog (mShh) protein, and upon introduction into a subject *in vivo*, did so in the murine distal small intestine and colon. This source of

Hedgehog protein was then tested for its ability to prevent cancer development. Several of the key experiments (not yet published) are reported below.

3. The LL bacteria were first shown to secrete the active 19 kDa N-terminal Shh polypeptide. See Figs. 1a and 1b of Appendix 1 to this Declaration.

4. The biological activity of the secreted mShh protein from the LL bacteria was demonstrated by the induction of alkaline phosphatase expression in C3H10T1/2 cells (Fig. 2). Culture supernatant of control (LL-EV) or mShh-secreting (LL-mShh) bacteria were examined in a standardized assay for Hedgehog protein activity (Katagiri *et al.*, 1990, *Biochem Biophys Res Commun* 172:295). Results show that the transgenic bacteria secreted significantly more biologically-active Shh than did the controls.

5. The effect of LL-mShh *in vivo* was examined in the small intestine of normal C57BL/6J mice after 7 days of once daily gastric inoculations with 250 μ L of a suspension of bacteria that had grown to saturation density. Results are shown in Fig. 3. The concentration of total¹ Hedgehog protein in whole lysates of different segments of the small intestine were measured and are expressed as ng/ml measured by ELISA with monoclonal antibody 5E1² that is cross-reactive for all 3 murine Hedgehog proteins (Sonic, Indian, Desert). The results show that LL-mShh significantly increased the concentration of total hedgehog protein in the distal small intestine (as compared to the proximal duodenum), with the highest concentration in the ileum.

6. Finally, we delivered these bacteria to *APC*^{+/min} mice by daily gavage, over a 4 week period, to test the ability of the Shh protein to prevent development of adenomatous polyps (murine model of FAP/sporadic colorectal carcinoma). These mice serve as an excellent model for GI tumor development of as they carry a heterozygous mutation in the *APC* gene which results in the formation of multiple adenomas, the precursors of adenocarcinomas, predominantly in the small intestine. This mutation affects the same gene as is affected in patients with familial adenomatous polyposis (FAP) and most sporadic colorectal carcinomas. The results are shown in Table 1 in Appendix 1. Administration of LL-mShh was found to prevent adenoma formation in the ileum (highly statistically significant), which is the site where most of recombinant mShh is secreted by the transformed bacteria (see ELISA results in Fig. 3).

¹ endogenously expressed plus exogenous, LL-mShh-delivered

² Pepinsky RB *et al.*, , 2000, *J Biol Chem.* 275:10995-1001; Ericson, J *et al.*, 1995, *Cell* 81:747-56; Hunt R, *et al.*, 2007, *Hybridoma* 26:231-40.

7. The foregoing results confirm what was described in the patent application - already conceived by me and my co-inventors by the time the priority application was prepared. A "source of Hedgehog protein," in this case, in the form of transgenic *Lactococcus lactis* bacteria secreting Shh, had the following actions:

- (a) The bacteria indeed secreted biologically active recombinant Shh protein;
- (b) Secretion of this protein occurred *in vivo* in the small intestine, primarily in the distal small intestine (ileum); and,
- (c) Most importantly, secretion of the recombinant Shh protein prevented the development of a form ("precursor") of GI cancer -- intestinal adenomas -- *in vivo*.

The application, together with these results, supports not only methods of treating cancer, but also supports methods for preventing G.I. cancer development.

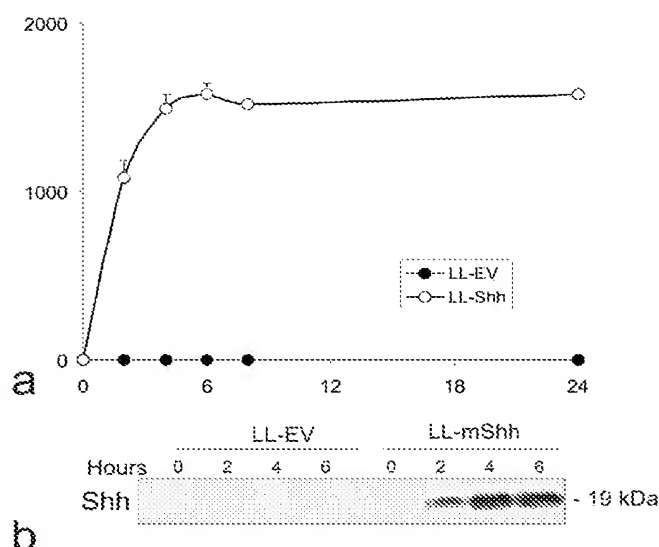
8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Date: April 29, 2008 /s/ Gijs Robert van den Brink

Gijs Robert van den Brink

APPENDIX 1

FIGURES AND TABLE



Figs 1a and 1b. Fig.1a shows a time course (hrs) of concentrations (ng/ml) of murine Shh in supernatants of (i) control empty vector carrying LL (LL-EV) and (ii) Shh secreting LL (LL-mShh) as determined in a Hedgehog protein-specific ELISA using a monoclonal antibody 5E1 that recognizes all three hedgehog proteins. **Fig. 1b** shows a Western blot analysis of murine Shh 19 kDa polypeptide expression measured in supernatants of cultures of LL-EV and LL-mShh bacteria using the above antibody.

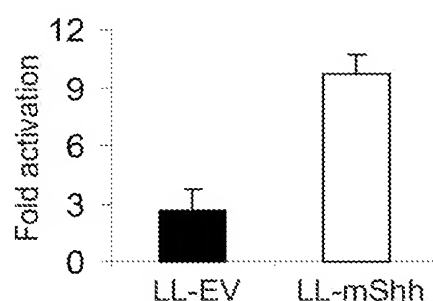


Fig. 2. mShh protein induces alkaline phosphatase expression in cells of the C3H10T1/2 line, measured as “fold-activation” of alkaline phosphatase (relative units). The effect of empty vectors (LL-EV) and Shh-secreting bacteria (LL-mShh) were compared. The assay used was a well-established assay of Hedgehog protein activity (Katagiri *et al. Biochem Biophys Res Commun* 1990;172:295).

APPENDIX 1

FIGURES AND TABLE

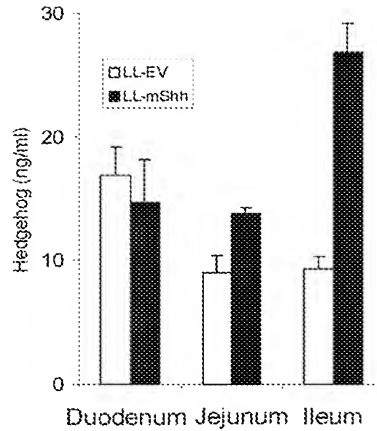


Fig. 3: Effect of LL-mShh *in vivo* in the small intestine of normal C57BL/6J mice after 7 days of once daily gastric inoculations with 250 µL of bacteria grown to saturation density (2×10^9 colony-forming units). Concentration of Hedgehog protein in whole lysates of different segments of the intestine (duodenum, jejunum, ileum) was measured by ELISA (using an antibody that recognizes all three hedgehog proteins).

Table 1

	Polyp number, 7 weeks	Polyp number, 11 weeks		New polyps during treatment	
		LL-EV	LL-mShh	LL-EV	LL-mShh
duodenum	1.0 ± 0.5	5.0 ± 1.0	5.7 ± 1.0	4.0 ± 1.0	4.7 ± 1.0
jejunum	7.8 ± 1.7	13.0 ± 3.4	9.8 ± 1.2	5.2 ± 3.2	2.0 ± 1.2
ileum	11.6 ± 2.4	24.6 ± 3.1	16.7 ± 1.8^a	13.0 ± 2.9	5.1 ± 1.8^a
colon	1.2 ± 0.5	1.2 ± 0.3	1.3 ± 0.3	0.0 ± 0.3	0.1 ± 0.3

^a $P = 0.01$ by student *t*-test, LL-mShh ($n = 12$) compared to LL-EV ($n = 11$)

7 week old *APC*^{+/min} mice were treated daily for four weeks by oral gavage with 250 µl of either LL-EV or LL-mShh grown to saturation density (see above). Polyps were enumerated as an estimate of the number of adenomas. Mice were sacrificed either at 7 weeks of age to determine the starting number of adenomas or after 4 weeks of daily treatment (“polyp number, 11 weeks”) to evaluate the effect of the treatment. Reduction in adenoma formation (number of adenomatous polyps) was greatest in the ileum.

APPENDIX 2

Curriculum Vitae of Gijs Robert van den Brink

Home address: 17bis Chemin de Frenes, 1295 Tannay, Switzerland
Tel: 0041-22-7768683
Work address: Department of Gastroenterology & Hepatology, Leiden University Medical Center,
Albinusdreef 2, 2333 ZA Leiden, Netherlands.
E- mail: g.r.van.den.brink@lumc.nl
Born: 06-08-1970

Professional Experience, Training and Education

Jan 2008 - **Chief, Laboratory of Gastroenterology & Hepatology**
Department of Gastroenterology & Hepatology
Leiden University Medical Center, Leiden, the Netherlands

Jan 2008 - July 2009 **Resident in Gastroenterology**
Department of Gastroenterology & Hepatology
Leiden University Medical Center, Leiden, the Netherlands

Jan 2006 - Jan 2008 Department of Gastroenterology & Hepatology
Geneva University Hospital, Geneva, Switzerland

Sep 2006 - Jan 2008 **Postdoctoral Fellow**
Laboratory of the Department of Gastroenterology & Hepatology
Leiden University Medical Center, Leiden, the Netherlands

Jan 2003 – Jan 2008 **Postdoctoral Fellow**
Department of Experimental Internal Medicine Academic Medical Center,
Amsterdam, the Netherlands
Department of Experimental Internal Medicine

Oct 2002-Oct 2005 **Resident in Internal Medicine**
Academic Medical Center, Amsterdam, the Netherlands
Department of Internal Medicine

Sep 1998-11 Dec 2002 **PhD, *cum laude*, University of Amsterdam**
Thesis entitled: "Morphostasis of the adult gastrointestinal tract".
Supervisors: Dr S.J. van Deventer and Dr M.P. Peppelenbosch

Oct 1989-24-02-98 **MD degree, University of Amsterdam**
Academic Medical Center, Amsterdam, The Netherlands

1983 – 1989 **Murmellius Gymnasium, Alkmaar, The Netherlands**

Further Professional Experience

March 2001-May 2001 **Harvard University, Boston, MA, USA**
Department of Pathology, Massachusetts General Hospital
Studied gut morphogenesis (chick model) in lab of Dr DJ Roberts.

Jan 2001 **DNAX Research Institute, Palo Alto, CA, USA**
Visiting scientist in the lab of Dr JD Sedgwick. Studied role of TNF in gastric hormone regulation

April 1998-Sep 1998 **Academic Medical Center, Amsterdam**
Department of Pediatric Gastroenterology and Nutrition.
Investigated determinants of the colonization pattern of *H. Pylori*.

Oct 1997- Dec 1997 **Academic Medical Center, Amsterdam**
Department of Gastroenterology. Set up prospective randomized trial assessing the need to use conscious sedation in endosonography

Aug 1994– Aug 1995 **New England Medical Center, Tufts University, Boston, MA, USA**
Department of Pediatric Gastroenterology. Investigated regulation of intestinal genes in intestinal differentiation..

1994 **Academic Medical Center, Amsterdam**
Department of Gastroenterology. Participated in trial of balloon dilatation of the sphincter of Oddi

Awards & Grants

- Oct 2008 **ASNEMGE “Rising Star” Award**
‘Rising star in Gastroenterology’ award at the 2008 United European Gastroenterology Week in Vienna.
- Dec 2007 **MLDS Grant**
Awarded € 130.000 for project entitled: ‘The role of Hedgehog signaling in colonic epithelial homeostasis’.
- Aug 2007 **Yearly Ferring Fellowship**
Awarded € 15.000/year to select one student per year to work in a lab specialized in IBD in the USA for a period of a year with a € 20.000 grant.
- Jan 2007 **Organon Grant**
Awarded € 283,791 for two year project that investigates the effect of sex hormones on colorectal cancer development.
- Jan 2007 **Ferring Grant**
Co-principle investigator on a € 93,930 two year project that will investigate the molecular mechanism of colitis associated colorectal carcinogenesis
- Jan 2007 **UCB Grant**
Co-principle investigator on a € 247,860 four year project that will investigate the mechanism of action of anti-TNF treatment in IBD
- Dec 2005 **VENI Grant**
Scored best project, NWO (Netherlands Organisation for Scientific Research) awarded € 200,000, for project entitled “Hedgehog signaling in colorectal carcinogenesis”
- Dec 2005 **PhD Student Grant:** Awarded € 200,000 by the Academic Medical Center, Amsterdam
- April 2003 **Emerging Leaders in Gastroenterology:** Invited member of a society that brings together young academic gastroenterologists from around the world.
- Aug 2002 **PhD Student Grant:** Awarded € 200,000 by the Academic Medical Center, Amsterdam
- 2005 **Netherlands Society for Gastroenterology**
Received “gastro start” € 7,000 grant that financed experiments that investigate the role of hedgehog signaling in colorectal carcinogenesis.
- 1994 **Glaxo Fellowship:** Awarded \$ 20,000 for one year fellowship in a laboratory in the U.S.

Invited Lectures

- Oct 2008 ‘Rising star in Gastroenterology’ Lecture, UEGW Vienna, Austria, 2008
- May 2008 ‘Rising star in Gastroenterology’ Lecture, Digestive Disease Week, San Diego, CA, USA
- Feb 2008 CNIO Cancer Conference, Centro Nacional de Investigaciones Oncológicas, Madrid, SPAIN
- Jan 2008 Institut für Humangenetik, Göttingen University, Göttingen, GERMANY
- Nov 2007 IBDnet Meeting, Barcelona, SPAIN
- April 2007 Oasis Lecture, AMC, Amsterdam
- Nov 2006 Journées de Gastroenterologie, Geneva, SWITZERLAND
- Oct 2006 EMBO workshop on Hedgehog-Gli Signaling in Cancer and Stem Cells, Rome, ITALY
- May 2006 Stowers Institute for Medical Research, Kansas City, MO, USA
- Jun 2006 Lundberg Laboratory, Goteborg University, Goteborg, SWEDEN
- Jan 2005 Invited speaker - Annual New Year’s speech of Board of Directors of the AMC
- July 2004 Breakfast Lecture, 10th Ann Meeting of Japanese Soc for Helicobacter Research, Tokyo
- Jan 2004 Karolinska Institute, Stockholm, SWEDEN.
- May 2003 “State of the Art” lecture at Current Topics in Gastroenterology, Faro, PORTUGAL.
- May 2002 Clevers Laboratory, Utrecht, the NETHERLANDS.
- May 2001 Department of Pathology Grand Rounds, Massachusetts General Hospital, Boston, USA.
- Jan 2001 DNAX Research Institute, Palo Alto, CA, USA.
- Nov 2000 Dept. of Cell Biology, Skirball Institute, NYU School of Medicine, New York, NY, USA.

LIST OF PUBLICATIONS

1. Bergman JJ, **Van den Brink GR**, Rauws EA, de Wit L, Obertop H, Huibregtse K, Tytgat GN, Gouma DJ. Treatment of bile duct lesions after laparoscopic cholecystectomy. **Gut**. 1996;38:141-7
2. **Van Den Brink GR**, Bloemers SM, Van Den Blink B, Tertoolen LG, Van Deventer SJ, Peppelenbosch MP. Study of calcium signaling in non-excitabile cells. **Microsc Res Tech**. 1999;46:418-33
3. **Van Den Brink GR**, ten Kate FJ, Ponsioen CY, Rive MM, Tytgat GN, van Deventer SJ, Peppelenbosch MP. Expression and activation of NF-kappa B in the antrum of the human stomach. **J Immunol**. 2000;164:3353-9
4. **Van den Brink GR**, Tytgat KM, Van der Hulst RW, Van der Loos CM, Einerhand AW, Buller HA, Dekker J. H pylori colocalises with MUC5AC in the human stomach. **Gut**. 2000;46:601-7
5. Versteeg HH, Nijhuis E, **Van den Brink GR**, Evertzen M, Pynaert GN, van Deventer SJ, Coffey PJ, Peppelenbosch MP. A new phosphospecific cell-based ELISA for p42/p44 mitogen-activated protein kinase (MAPK), p38 MAPK, protein kinase B and cAMP-response-element-binding protein. **Biochem J**. 2000;350 Pt 3:717-22.
6. **Van den Brink GR**, O'Toole T, Hardwick JC, van den Boogaardt DE, Versteeg HH, van Deventer SJ, Peppelenbosch MP. Leptin signaling in human peripheral blood mononuclear cells, activation of p38 and p42/44 mitogen-activated protein (MAP) kinase and p70 S6 kinase. **Mol Cell Biol Res Commun**. 2000;4:144-50.
7. Hardwick JC, **Van den Brink GR**, Offerhaus GJ, van Deventer SJ, Peppelenbosch MP. NF-kappaB, p38 MAPK and JNK are highly expressed and active in the stroma of human colonic adenomatous polyps. **Oncogene**. 2001;20:819-27.
8. Hardwick JC, **Van Den Brink GR**, Offerhaus GJ, Van Deventer SJ, Peppelenbosch MP. Leptin is a growth factor for colonic epithelial cells. **Gastroenterology**. 2001;121:79-90.
9. **Van den Brink GR**, Hardwick JC, Tytgat GN, Brink MA, Ten Kate FJ, Van Deventer SJ, Peppelenbosch MP. Sonic hedgehog regulates gastric gland morphogenesis in man and mouse. **Gastroenterology**. 2001;121:317-28.
10. **Van Den Brink GR**, de Santa Barbara P, Roberts DJ. Epithelial cell differentiation-a Mather of choice. **Science**. 2001;294(5549):2115-6.
11. **Van den Brink GR**, van den Boogaardt DE, van Deventer SJ, Peppelenbosch MP. Feed a cold, starve a fever? **Clin Diagn Lab Immunol**. 2002;9:182-3.
12. **Van den Brink GR**, Hardwick JC, Nielsen C, Xu C, ten Kate FJ, Glickman J, van Deventer SJ, Roberts DJ, Peppelenbosch MP. Sonic hedgehog expression correlates with fundic gland differentiation in the adult gastrointestinal tract. **Gut**. 2002;51:628-33.
13. Van Den Blink B, Ten Hove T, **Van Den Brink GR**, Peppelenbosch MP, Van Deventer SJ. From extracellular to intracellular targets, inhibiting MAP kinases in treatment of Crohn's disease. **Ann N Y Acad Sci**. 2002;973:349-58.
14. de Santa Barbara P, **Van den Brink GR**, Roberts DJ. Molecular etiology of gut malformations and diseases. **Am J Med Genet**. 2002;115:221-30.
15. Bonta PI, Kok MF, Bergman JJ, **Van den Brink GR**, Lemkes JS, Tytgat GN, Fockens P. Conscious sedation for EUS of the esophagus and stomach: a double-blind, randomized, controlled trial comparing midazolam with placebo. **Gastrointest Endosc**. 2003;57:842-7.
16. Van den Brande JM, Braat H, **Van den Brink GR**, Versteeg HH, Bauer CA, Hoedemaeker I, van Montfrans C, Hommes DW, Peppelenbosch MP, van Deventer SJ. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. **Gastroenterology**. 2003;124:1774-85.
17. de Santa Barbara P, **Van den Brink GR**, Roberts DJ. Development and differentiation of the intestinal epithelium. **Cell Mol Life Sci**. 2003;60:1322-32.
18. Hardwick JC, **Van Den Brink GR**, Bleuming SA, Ballester I, Van Den Brande JM, Keller JJ, Offerhaus GJ, Van Deventer SJ, Peppelenbosch MP. Bone morphogenetic protein 2 is expressed by, and acts upon, mature epithelial cells in the colon. **Gastroenterology**. 2004;126:111-21.
19. **Van den Brink GR**, Bleuming SA, Hardwick JC, Schepman BL, Offerhaus GJ, Keller JJ, Nielsen C, Gaffield W, van Deventer SJ, Roberts DJ, Peppelenbosch MP. Indian Hedgehog is an antagonist of Wnt signaling in colonic epithelial cell differentiation. **Nat Genet**. 2004;36(3):277-82.
20. Hardwick JC, van Santen M, **Van den Brink GR**, van Deventer SJ, Peppelenbosch MP. DNA array analysis of the effects of aspirin on colon cancer cells: involvement of Rac1. **Carcinogenesis**. 2004;25(7):1293-8.
21. Bleuming SA, Peppelenbosch MP, Roberts DJ, **Van den Brink GR**. Homeostasis of the adult colonic epithelium: a role for morphogens. **Scand J Gastroenterol**. 2004;39(2):93-8
22. Verhave M, Krasinski SD, Christian SI, Van Schaik S, **Van Den Brink GR**, Doting EM, Maas SM, Wolthers KC, Grand RJ, Montgomery RK. Regulatory regions in the rat lactase-phlorizin hydrolase gene that control cell-specific expression. **J Pediatr Gastroenterol Nutr**. 2004;39(3):275-85.

23. **Van den Brink GR.** Linking pathways in colorectal cancer. **Nat Genet.** 2004;36:1038-9.
24. Nielsen CM, Williams J, **Van den Brink GR**, Lauwers GY, Roberts DJ. Hh pathway expression in human gut tissues and in inflammatory gut diseases. **Lab Invest.** 2004;84:1631-42.
25. Suzuki H, Minegishi Y, Nomoto Y, Ota T, Masaoka T, **Van den Brink GR**, Hibi T. Down-regulation of a morphogen (sonic hedgehog) gradient in the gastric epithelium of *Helicobacter pylori*-infected Mongolian gerbils. **J Pathol.** 2005;206(2):186-97.
26. **Van Den Brink GR**, Peppelenbosch MP. Expression of hedgehog pathway components in the adult colon. **Gastroenterology.** 2006;130(2):619.
27. Bleuming SA, Kodach LL, Garcia Leon MJ, Richel DJ, Peppelenbosch MP, Reitsma PH, Hardwick JC, **Van den Brink GR.** Altered Bone Morphogenetic Protein signaling in the *Helicobacter pylori* infected stomach. **J Pathol,** 2006;209:190-7.
28. **Van den Brink GR**, Hardwick JC. Hedgehog Wnteraction in colorectal cancer. **Gut,** 2006;55:912-4.
29. Bos CL, Kodach LL, **Van den Brink GR**, Diks SH, Van Santen MM, Richel DJ, Peppelenbosch MP, Hardwick JCH. Effect of Aspirin on the Wnt/ β -catenin pathway is mediated via Protein Phosphatase 2A. **Oncogene,** 2006;25:6447-56.
30. Xu CP, Ji WM, **van den Brink GR**, Peppelenbosch MP. Bone morphogenetic protein-2 is a negative regulator of hepatocyte proliferation downregulated in the regenerating liver. **World J Gastroenterol.** 2006;12:7621-5.
31. **Van den Brink GR**, Offerhaus GJ. The morphogenetic code and colon cancer development. **Cancer Cell,** 2007;11:109-117
32. Lowenberg M, Verhaar A, **Van den Brink GR**, Hommes DW. Glucocorticoid signaling: a nongenomic mechanism for T-cell immunosuppression. **Trends Mol Med,** 2007;13:158-63
33. Bleuming SA, He XC, Kodach LL, Hardwick JC, Koopman FA, Ten Kate FJ, Van Deventer SJ, Hommes DW, Peppelenbosch MP, Offerhaus GJ, Li L, **Van den Brink GR.** Bone Morphogenetic Protein signaling suppresses tumorigenesis at gastric epithelial transition zones in mice. **Cancer Res,** 2007;67:8149-55.
34. **Van den Brink GR.** Hedgehog signaling in development and homeostasis of the gastrointestinal tract. **Physiol Rev,** 2007;87:1343-75.
35. Kodach LL, Bleuming SA, Peppelenbosch MP, Hommes DW, **Van den Brink GR**, Hardwick JC. The effect of statins in colorectal cancer is mediated through the Bone Morphogenetic Protein pathway. **Gastroenterology,** 2007;133:1272-81.
36. Van den Berg A, Van Elburg RA, Vermeij L, Van Zwol A, **Van den Brink GR**, Twisk JW, Nieuwenhuis EE, Fetter W. Cytokine responses in very low birth weight infants receiving glutamine-enriched-enteral nutrition **J Pediatr Gastroenterol Nutr,** in press.
37. Kodach LL, Bleuming SA, Musler AR, Peppelenbosch MP, Hommes DW, **Van den Brink GR**, Van Noesel CJ, Offerhaus GJ, Hardwick JC. The Bone Morphogenetic Protein Pathway is active in human colon adenomas and inactivated in colorectal cancer. **Cancer,** 2008;112:300-6.
38. Kodach LL, Wiercinska E, de Miranda NF, Bleuming SA, Musler AR; Peppelenbosch MP, Dekker E, **van den Brink GR**, van Noesel CJ, Morreau H, ten Dijke P, Offerhaus GJ, Hardwick JC. The Bone Morphogenetic Protein Pathway is inactivated in the majority of Sporadic Colorectal Cancers. **Gastroenterology,** 2008, in press.
39. Duijvestein M, **van den Brink GR**, Hommes DW. Stem cells as potential novel therapeutic strategy for inflammatory bowel disease. **J Crohn's Colitis,** 2008, in press.
40. Barros R, Pereira B, Duluc I, Azevedo M, Mendes N, Paulo P, Santos-Silva F, van Seuningen I, **van den Brink GR**, David L, Freund JN, Almeida R. Key elements of the BMP/SMAD pathway colocalize with Cdx-2 in intestinal metaplasia and regulate Cdx-2 expression in human gastric cell lines. **J Pathol.** In press.

Book Chapters

J Dekker, BJ van Klinken, KAMJ Tytgat, **GR van den Brink**, JHB van de Bovenkamp, M Verburg, IB Renes, HA Büller, AWC Einerhand. Regulation of mucin expression in the gastrointestinal tract. In: **Digestive mucus: from research to clinical implications.** J Bara, *et al.*, eds. Irvin editions, Neuilly-sur-Seine 2000.

GR van den Brink, MP Peppelenbosch, DJ Roberts. Hedgehog signaling in gastrointestinal morphogenesis and morphostasis. In : **Physiology of the GI Tract**, 4th edition.